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Review article

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Invasive and medical management approaches to non-acute myocardial ischaemic syndromes

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Abstract

Over the past two decades, approaches to managing patients with coronary artery disease have improved substantially with advances in percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, pharmacological secondary prevention, anti-anginal agents and lifestyle interventions. Accordingly, clinical management choices in non-acute myocardial ischaemic syndromes (NAMIS) remain a timely and important topic. The risks and benefits of an invasive strategy combined with optimal medical therapy (OMT) versus a conservative strategy of OMT alone should be discussed with patients to facilitate shared clinical decision making. The findings from high-quality, randomized, controlled trials in the era of modern OMT form an essential platform for these informed conversations. In totality, the evidence from randomized, controlled trials supports OMT as the first-line therapeutic approach in patients with NAMIS, whereas selected patients at high anatomical risk or those with persistent anginal symptoms despite initial OMT often derive further symptom relief from invasive therapy with PCI. In patients with high-risk NAMIS, including those with multivessel disease and diabetes mellitus, CABG surgery improves survival, whereas the benefit is less clear for PCI. In this Review, we discuss the findings from contemporary trials evaluating outcomes in patients with NAMIS treated invasively or conservatively with OMT alone, and we conclude with proposed management pathways.

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Key points

- The available evidence supports the optimization of medical therapy as the first-line therapeutic approach for most patients with non-acute myocardial ischaemic syndromes.
- Physicians should carefully consider selected patients who might benefit from invasive therapy with percutaneous coronary intervention or coronary artery bypass graft surgery.
- Patients with persistent symptoms who are unable to tolerate up-titration of medications might be candidates for early percutaneous coronary intervention to improve symptoms, especially for non-complex coronary artery disease.
- Selecting appropriate high-risk patients who would benefit from coronary artery bypass graft surgery continues to be supported by the evidence for improved event-free survival.
- Prospective studies are warranted both to define subsets of patients with non-acute myocardial ischaemic syndromes who might benefit from invasive therapies and to elucidate the mechanisms by which benefit is derived.
- The totality of trial-based evidence points towards the need for physicians and patients to engage in shared clinical decision making on whether to proceed with invasive management.

Introduction

Cardiovascular disease accounts for 30% of all deaths globally, with 7.3 million due to coronary artery disease (CAD) alone[1], making it the leading cause of death and disability worldwide[2]. The term non-acute myocardial ischaemic syndromes (NAMIS) was proposed in 2024 (ref. 3) as a unifying nomenclature to replace conflicting terminology, such as stable CAD, stable ischaemic heart disease, chronic coronary syndromes and chronic coronary disease (Box 1). This new nomenclature was introduced with the goals of encompassing the various pathophysiological causes and triggers of both angina pectoris and myocardial ischaemia, and harmonizing the competing classifications used in the medical literature and across international clinical practice guidelines. We recognize that this terminology is still evolving and therefore present it as a unifying descriptive framework, rather than a prescriptive standard. To promote consistency and inclusivity of classification, we refer to NAMIS throughout this Review.

In 1958, F. Mason Sones laid the foundations for the identification of obstructive epicardial coronary lesions with his seminal use of invasive coronary angiography[4]. As a consequence, the ability to intervene favourably on obstructive, flow-limiting coronary stenoses — first with coronary artery bypass graft (CABG) surgery in the 1960s, and then with percutaneous coronary intervention (PCI) in 1977 — has revolutionized cardiovascular therapeutics. Robust data derived from multiple randomized, controlled clinical trials (RCTs) support the unambiguous benefits of invasive therapy (primarily PCI) for most cases of acute coronary syndrome (ACS) and acute myocardial infarction (MI) on an urgent or emergent basis[5–8]. However, whether PCI of flow-limiting coronary stenoses reduces mortality or the incidence acute MI in patients with NAMIS has not been conclusively established to date. By contrast, CABG surgery has led to a consistent and significant reduction in spontaneous MI among these patients, which can also be accompanied by a prolongation of life expectancy in selected subgroups of patients with high-risk NAMIS[9–15].

Notably, over the past few decades, substantial advances have been made in both invasive treatment (PCI and CABG surgery) and medical therapy. The latter includes disease-modifying medications to reduce thrombotic, dyslipidaemic, metabolic and inflammatory risk, as well as anti-anginal agents for symptom control. In aggregate, intensive pharmacotherapy to control cardiac risk factors and symptoms is often referred to as 'optimal medical therapy' (OMT)[16]. Therefore, the clinical management of individual patients with NAMIS continues to evolve as new and increasingly effective procedural and pharmacological approaches become available. Importantly, clinicians must consider how best to conduct a shared decision-making process that highlights the risks and benefits of an invasive strategy combined with OMT versus a conservative strategy of OMT alone. Within just the past decade, the armamentarium of OMT has proliferated and improved, making decisions on procedural intervention increasingly nuanced in a patient population with heterogeneous cardiovascular risk profiles and variable risk tolerance. In addition, the publication of several RCTs — most notably FAME 3 (ref. 11), ISCHEMIA[17,18], ISCHEMIA-EXTEND[19], REVIVED-BCIS2 (ref. 20), STICH[21,22], STICHES[23], ORBITA[24], ORBITA-2 (ref. 25) and PREVENT[26] — has added further evidence to the existing literature that will inform therapeutic choices for all stakeholders.

With this background, the objective of this Review is to provide physicians with an updated assessment of the contemporary evidence and help to guide shared decision making in patients with NAMIS. Our aims are to summarize the current evidence base for OMT with or without PCI or CABG surgery; examine the effect of PCI, CABG surgery and OMT on mortality and cardiovascular event reduction, as well as symptom control and quality of life (QoL); discuss the role of invasive treatment for various subgroups of patients, focusing on those with symptomatic left main CAD (LMCAD), multivessel CAD, left ventricular (LV) systolic dysfunction and diabetes mellitus; and contrast the effects of OMT with or without invasive treatment on the control of anginal symptoms and QoL.

Invasive versus medical management

Mortality and cardiovascular events

Since the 1970s, many practitioners of cardiovascular medicine have firmly believed that catheter-based or surgical treatment of flow-limiting coronary stenoses, regardless of the acuity in clinical presentation or symptoms, could reduce or prevent incident MI and cardiovascular death. This belief was anchored in the so-called oculostenotic reflex, by which a severe epicardial coronary stenosis identified using angiography is implicitly assumed to be the proximate cause of angina, myocardial ischaemia and eventual MI[27]. Both the short-term and the long-term clinical benefits of PCI in the majority of patients with ACS (including most presentations of acute myocardial ischaemic syndrome) are important and indisputable. However, whether PCI reduces cardiovascular events and mortality in patients with NAMIS is much less clear. Multiple systematic reviews and meta-analyses of large, contemporary RCTs have not demonstrated a reduction in these end points in patients with NAMIS[12,28–30]. A timeline of RCTs in which revascularization was compared with medical therapy is shown in Fig. 1, with the details of these trials provided in Tables 1 and 2. Figure 2 shows a timeline of trials in which CABG surgery was compared with PCI, medical therapy or both, and the details of these trials are provided in Table 3.

Early trials in the pre-stent era. Before the availability of modern, multifaceted OMT in the current millennium, RCTs dating back to the single-site MASS trial[31] published in 1995 showed that, among patients with stable angina, there was no significant difference in the composite outcome of death or MI among those undergoing PCI versus medical therapy. A series of subsequent trials confirmed the lack of a reduction in mortality with PCI in patients with NAMIS, including the RITA-2 trial[32] in 1997 involving 1,018 patients with CAD who were randomly assigned to either balloon angioplasty or rudimentary medical therapy consisting of only β-blockers and nitrates — both clearly outmoded approaches by today's standard. This early trial from the pre-stent era showed that there was a significantly greater risk of death or non-fatal MI in patients treated with angioplasty compared with the limited contemporaneous medical therapy (mean follow-up 2.7 years)[32]. However, the subsequent long-term analysis (7 years) showed no significant difference in the rates of death or MI between the two groups[33]. The AVERT trial[34] demonstrated the benefits of medical therapy with high-dose atorvastatin (80 mg daily) versus balloon angioplasty in patients with NAMIS and elevated plasma levels of LDL cholesterol. Patients were found to have a lower incidence of ischaemic events with 'intensive' lipid lowering alone.

Small trials of CABG surgery or PCI versus medical therapy in the 1980s showed some potential evidence of increased survival with invasive treatment, although these trials did not uniformly separate CABG surgery from PCI in assessing treatment effectiveness. Notably, clinical outcomes are potentially influenced by important treatment differences between the two techniques — CABG surgery has a much greater effect than PCI on prevention of future MI — which are specifically relevant in patients with NAMIS[9]. Other small trials, including the ACIP trial[35] published in 1997, suggested improvements with invasive treatment compared with angina-guided medical therapy, but were not designed to have sufficient statistical power to detect significant differences in clinical outcomes. Importantly, in all these early RCTs, medical therapy was assessed solely in comparison with PCI.

The introduction of bare-metal stents. The COURAGE trial[36] (2007) was the first RCT to test the hypothesis that PCI plus OMT has incremental clinical benefit over OMT alone. In this study, 2,287 patients with NAMIS and clinically significant anatomical CAD were randomly assigned to either OMT plus PCI (bare-metal stents (BMS) were used in 97% of participants) or multifaceted OMT alone. PCI was not associated with a significant reduction in mortality, MI or other cardiovascular events compared with OMT[36]. These findings were confirmed in a subsequent analysis performed after 15 years of follow-up, which showed no significant difference in survival between the two groups[37]. In 2009, the BARI 2D Study Group published the results of another large RCT, involving 2,368 patients with type 2 diabetes and NAMIS who were randomly assigned to either PCI (65% received BMS and 35% received drug-eluting stents (DES)) or CABG surgery with OMT versus OMT alone[38]. This study built on the findings of the original BARI trial[39], which demonstrated increased survival with CABG surgery compared with PCI in patients with diabetes and multivessel disease (19% of the total trial population). In the BARI 2D trial[38] there were no significant differences in the rates of death or major adverse cardiovascular events between the groups. However, the prespecified secondary composite end point of death, MI or stroke was significantly reduced in patients who underwent CABG surgery plus OMT compared with OMT alone, a finding driven largely by a reduction in the incidence of MI. In patients with diabetes, including those with a baseline elevation in plasma troponin levels, treatment with PCI plus OMT produced no significant benefit over OMT alone[38,40]. Importantly, CABG surgery and PCI have different treatment effects, and trials assessing the effect of invasive treatment by combining both interventions can dilute or mask potential benefits derived specifically from CABG surgery in high-risk subgroups of patients with NAMIS.

The advent of DES and imaging-guided PCI. After the publications of the COURAGE[36] and BARI 2D[38] trials, the landscape of PCI evolved substantially with the advent of DES, which reduced restenosis, recurrent angina and the need for subsequent revascularization in patients with NAMIS. Moreover, in many early trials, PCI did not routinely incorporate physiology-guided lesion selection or intravascular imaging optimization, which might have influenced the observed outcomes. This evolution in PCI prompted the cardiovascular community to question whether equipoise continued to exist in real-world practice between invasive versus medical management strategies.

In the FAME 2 trial[41], which was published in 2012 after the routine use of DES was established, fractional flow reserve (FFR)-guided PCI plus OMT decreased the incidence of urgent revascularization compared with OMT alone in patients with NAMIS. However, only 888 out of a planned 1,600 patients were randomly assigned before the trial was terminated prematurely when the primary end point (a composite of death, MI or unplanned revascularization) showed superiority for PCI, a finding driven entirely by the revascularization component[41]. Several factors were cited to explain the differences in outcome in the FAME 2 trial compared with earlier trials, including the incidence of ischaemia. For example, in the COURAGE trial[36], fewer than one-third of patients had >10% ischaemia on myocardial perfusion imaging, whereas in the FAME 2 trial, the low mean FFR value of 0.68 indicated that most patients had large areas of myocardium at risk of ischaemia[41]. Additionally, randomization after diagnostic coronary angiography in the COURAGE and BARI-2D trials could have led to potential selection bias whereby the patients at highest risk, particularly those with the most critical or proximal lesions, could have been excluded in an open-label trial design[42]. Additional limitations in the COURAGE trial, including patient selection and procedural techniques, have been noted and might also have limited the generalizability of its

Box 1 | Unifying nomenclature for myocardial ischaemic syndromes

Current nomenclature

Coronary syndromes

- Acute: acute coronary syndromes (ACS) in American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) guidelines
- Chronic: chronic coronary disease in AHA/ACC guidelines; chronic coronary syndromes in ESC guidelines

New nomenclature

Myocardial ischaemic syndromes

- Acute myocardial ischaemic syndromes (AMIS): ACS caused by plaque erosion or rupture, or myocardial infarction with non-obstructive coronary arteries (MINOCA)
- Non-acute myocardial ischaemic syndromes (NAMIS): ischaemia caused by epicardial coronary stenoses, or ischaemia with non-obstructive coronary arteries (INOCA)

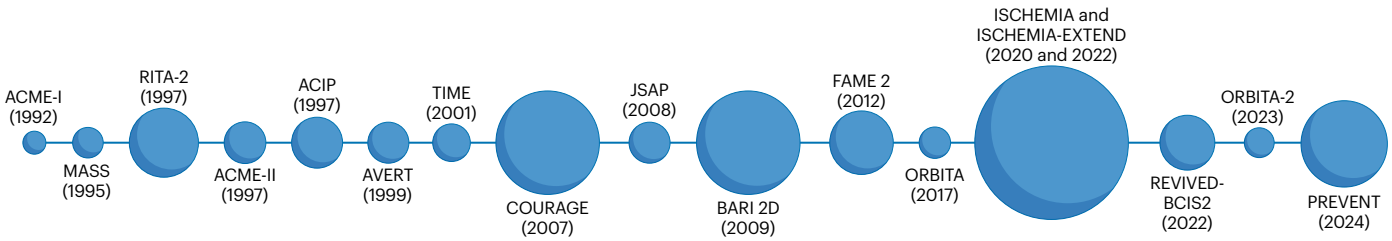

Fig. 1 | Timeline of trials in which revascularization was compared with medical therapy in patients with non-acute myocardial ischaemic syndromes. Randomized, controlled trials evaluating revascularization versus medical therapy are presented chronologically. The size of each circle is proportional to the sample size of the trial. ACIP[35], Asymptomatic Cardiac Ischemia Pilot; ACME-I[51] and ACME-II[88], Angioplasty Compared to Medicine-I/II; AVERT[34], Atorvastatin versus Revascularization Treatments; BARI 2D[38], Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE[36], Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; FAME 2 (ref. 41), Fractional Flow Reserve versus Angiography for Multivessel Evaluation; ISCHEMIA[17], International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; ISCHEMIA-EXTEND[19], International Study of Comparative Health Effectiveness with Medical and Invasive Approaches ongoing long-term follow-up; JSAP[87], Japanese Stable Angina Pectoris Study; MASS[31], Medicine, Angioplasty, or Surgery Study; ORBITA[24], Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; PREVENT[26], Preventive PCI or Medical Therapy Alone for Vulnerable Atherosclerotic Coronary Plaque; REVIVED-BCIS2 (ref. 20), Revascularization for Ischaemic Ventricular Dysfunction; RITA-2 (ref. 32), Randomized Intervention Treatment of Angina-2; TIME[52], Trial of Invasive vs Medical therapy in Elderly patients.

findings[43]. Additionally, the FFR-guided PCI approach in the FAME 2 trial was performed solely in lesions with an FFR of ≤0.80, suggesting that only functionally significant lesions benefit from PCI, as opposed to lesions treated primarily on the basis of angiographic findings, as shown in the BARI 2D trial. The 5-year follow-up analysis from the FAME 2 trial[44] showed a lower rate of the primary composite end point for FFR-guided PCI, but there was still no conclusive evidence for reductions in long-term mortality or the incidence of MI.

The limitations of earlier trials led to sufficient therapeutic uncertainty and equipoise to undertake a definitive RCT in patients with NAMIS and moderate-to-severe ischaemia at baseline in a much larger, international population. Accordingly, in the ISCHEMIA trial[17], 5,179 patients with moderate or severe reversible ischaemia, from 320 sites in 37 countries, were randomly assigned to either an invasive strategy (coronary angiography and intervention when feasible) plus OMT or to OMT alone. Importantly, >75% of patients who were revascularized in the ISCHEMIA trial underwent PCI rather than CABG surgery, and the choice of intervention was at the discretion of local heart teams. Although FFR was strongly encouraged, it was not mandated, and sites were provided with guidelines for performing PCI, including the use of FFR when available and appropriate. Importantly, patients with minimal or no angiographic disease and patients with LMCAD were excluded from the trial. Overall, the ISCHEMIA trial likewise did not show significant differences in the composite primary outcome (death from cardiovascular causes, MI or hospitalization for unstable angina, heart failure or resuscitated cardiac arrest) or secondary outcomes (death from cardiovascular causes or MI)[17]. In the ISCHEMIA-EXTEND analysis[19] (7 years of follow-up) published in 2022, cardiovascular mortality was lower in the invasive treatment group than in the OMT alone group, but non-cardiovascular mortality was higher, meaning that the probability of overall survival at 7 years did not differ significantly between the groups. The causes of the increase in non-cardiovascular deaths were not well defined, but increased rates of malignancy, potentially from radiation exposure[45], and increased inflammatory response to DES, have been postulated[46].

The ISCHEMIA trial also highlighted that anatomically complex and severe anatomical CAD (modified Duke prognostic index 6) were associated with the highest rate of MI or cardiovascular death at 4 years, whereas the extent and severity of ischaemia at baseline was not[47,48]. Despite the lack of significant differences in end points in the ISCHEMIA trial, debate continues as to whether OMT achieves similar outcomes to those of PCI in patients with high-risk NAMIS, such as those with LMCAD or those with an LV ejection fraction (LVEF) of <35%, who were excluded from this study. High-risk subgroups are discussed in more detail later in this Review (section Invasive therapy in high-risk subgroups). In the ISCHEMIA-EXTEND analysis[19], the event curves for spontaneous MI continued to diverge in favour of the invasive strategy, suggesting that benefits in terms of a reduction in spontaneous MI might accrue over time. This finding, in conjunction with the importance of anatomical CAD severity, underscores the need to further investigate the underlying mechanisms driving these observations[19]. In short, the available evidence derived from multiple RCTs shows an overall lack of clinical benefit for PCI with either BMS and DES on mortality and cardiovascular event reduction in patients with NAMIS. In addition, CABG surgery seems to increase survival in patients with NAMIS, specifically in those at high risk of future 'spontaneous' MI, such as those with extensive multivessel disease or diabetes[10,49].

Symptom control and quality of life

Although the prolongation of life expectancy in patients with NAMIS has been demonstrated only with CABG surgery[12,23], there is little debate about the superiority of any invasive treatment for reducing angina, increasing exercise time and improving overall QoL[50]. Details of trials assessing these end points are shown in Table 2.

As early as 1992 in the ACME-I trial[51], PCI was shown to significantly improve both the duration of exercise time free from angina and total exercise duration at 6 months compared with limited medical therapy (β-blockers and nitrates). In 1997, the much larger RITA-2 trial[32] also showed a greater improvement in anginal symptoms and total exercise time for balloon angioplasty than for medical therapy. The benefits of invasive intervention for angina relief were further replicated in older adults (aged ≥75% years) in the TIME trial[52] published in 2001. At 6-month follow-up, angina severity and QoL had improved to a significantly greater extent in the group assigned to invasive treatment than

Table 1 | Trials of invasive therapy compared with OMT in patients with NAMIS (mortality and cardiovascular end points)

Trial (year)	Key inclusion criteria	Intervention	Primary outcome measures	Primary outcome point estimates	Ref.
MASS (1995)	Patients (n=214) with stable angina, single-vessel disease with ≥80% stenosis in the LAD artery prior to first diagonal artery	Balloon angioplasty vs CABG surgery using the LIMA vs medical therapy	Composite of cardiac death, MI or refractory angina needing revascularization	Primary end point: 25% for angioplasty, 3% for CABG surgery, 17% for medical therapy (angioplasty vs CABG surgery, P=0.0002; CABG surgery vs medical therapy, P=0.006; angioplasty vs medical therapy, P=0.28)	31
RITA-2 (1997)	Patients (n=1,018) aged ≥18 years with clinically significant stenosis in ≥1 major epicardial vessel	Balloon angioplasty vs medical therapy	Composite of death and non-fatal MI	Primary end point: 6.3% for angioplasty vs 3.3% for medical therapy (absolute difference 3.0%, 95% CI 0.4–5.7%; P=0.02)	32
ACIP (1997)	Patients (n=558) with angiographically CAD suitable for revascularization (≥50% stenosis in ≥1 vessel or branch), ischaemia while exercising or in pharmacological stress testing and ≥1 episode of asymptomatic ischaemia in 48 h ECG monitoring, angina-free and symptom-free with medical therapy	Revascularization (PCI or CABG surgery) vs angina-guided medical therapy vs ischaemia-guided medical therapy	Hierarchical testing: (1) death, (2) death or MI, (3) death, MI or hospitalization for a cardiac condition	Death: 6.6% for angina-guided therapy, 4.4% for ischaemia-guided therapy, 1.1% for revascularization (P<0.02) Death or MI: 12.1% for angina-guided therapy, 8.8% for ischaemia-guided therapy, 4.7% for revascularization (P<0.04) Death, MI or recurrent hospitalization: 41.8% for angina-guided therapy, 38.5% for ischaemia-guided therapy, 23.1% for revascularization (P<0.001)	35
AVERT (1999)	Patients (n=341) with stable CAD, LDL cholesterol level ≥115 mg/dl, triglyceride level ≤500 mg/dl, ≥50% stenosis in ≥1 vessel, asymptomatic or with CCS class I or II angina, able to complete ≥4 min of treadmill test or bicycle exercise test at 20 W/min with no marked ischaemic ECG changes	PCI vs medical therapy with atorvastatin	Composite of death from cardiovascular causes, resuscitation after cardiac arrest, non-fatal MI, CVA, CABG surgery, angioplasty and worsening angina resulting in hospitalization	Primary end point: 13% for atorvastatin and 21% for PCI (P=0.048; NS after interim analyses adjustment)	34
TIME (2001)	Patients (n=305) aged ≥75 years with chest pain refractory to ≥2 anti-anginal agents irrespective of previous revascularization	Revascularization (PCI or CABG surgery) vs medical therapy	Composite of death, non-fatal MI and hospital admission for worsening or unstable angina (ACS) with or without the need for revascularization after 6 months	Primary end point: 19% for revascularization and 49% for medical therapy (P<0.0001)	52
COURAGE (2007)	Patients (n=2,287) with stable CAD, initial CCS class IV angina stabilized medically, and either (1) ≥70% stenosis in ≥1 vessel with objective ischaemia (either substantial ST segment depression or T wave inversion or inducible ischaemia with exercise or pharmacological stress) or (2) ≥1 stenosis of ≥80% and classic angina without provocative testing	PCI plus OMT vs OMT alone	Composite of death from any cause and non-fatal MI	Primary end point: 19.0% for PCI and 18.5% for OMT (unadjusted HR for PCI 1.05, 95% CI 0.87–1.27; P=0.62)	36
JSAP (2008)	Patients (n=384) aged 30–75 years with stable low-risk CAD with one-vessel or two-vessel disease (significant stenosis of ≥75% or ≥60% on quantitative CAG) indication for PCI based on vessel lesion and objective myocardial ischaemia	PCI plus OMT vs OMT alone	Death (total, cardiac or sudden) and death or ACS	Death: no significant difference between PCI and medical therapy (HR 0.87, 95% CI 0.28–2.60; P=0.79) Death or ACS: in favour of PCI (HR 0.474, 95% CI 0.24–0.88; P=0.019)	87
BARI 2D (2009)	Patients (n=2,368) with T2DM and CAD on angiography (≥50% stenosis with positive stress test or ≥70% stenosis and classic angina), all patients candidates for PCI or CABG surgery	Revascularization (PCI or CABG surgery) vs OMT	Primary: death from any cause Secondary: composite of death, MI or stroke	5-year survival: 88.3% for revascularization vs 87.8% for OMT group (P=0.97) In CABG surgery stratum: 22.4% for revascularization vs 30.5% for OMT group (P=0.01; P=0.002 for interaction between stratum and study group) In PCI stratum: no significant difference between revascularization and OMT	38
FAME 2 (2012)	Patients (n=888) with stable one-vessel, two-vessel or three-vessel disease suitable for PCI with ≥1 stenosis with FFR ≤0.80	FFR-guided PCI plus OMT vs OMT alone	Composite of death from any cause, non-fatal MI or unplanned hospitalization leading to urgent revascularization in first 2 years	Primary end point: 4.3% for PCI vs 12.7% for OMT (HR 0.32, 95% CI 0.19–0.53; P<0.001) Difference driven by lower rate of urgent revascularization in PCI group (1.6% vs 11.1%; HR 0.13, 95% CI 0.06–0.30; P<0.001)	41

Table 1 (continued) | Trials of invasive therapy compared with OMT in patients with NAMIS (mortality and cardiovascular end points)

Trial (year)	Key inclusion criteria	Intervention	Primary outcome measures	Primary outcome point estimates	Ref.
ISCHEMIA (2020)	Patients (*n*=5,179) with stable CAD and moderate or severe reversible ischaemia on imaging stress or severe ischaemia on exercise stress tests	PCI plus OMT (invasive) vs OMT alone (conservative)	Composite of death from cardiovascular causes, MI or hospitalization for unstable angina, heart failure or resuscitated cardiac arrest	Primary end point at 6 months: 5.3% for invasive therapy and 3.4% for conservative therapy (difference 1.9%, 95% CI 0.8–3.0%) Primary end point at 5 years: 16.4% for invasive therapy and 18.2% for conservative therapy (difference −1.8%, 95% CI −4.7 to 1.0%)	17
ISCHEMIA-EXTEND (2022)	Patients (*n*=5,179) with stable CAD and moderate or severe reversible ischaemia on imaging stress or severe ischaemia on exercise stress tests	PCI plus OMT (invasive) vs OMT alone (conservative)	All-cause, cardiovascular and non-cardiovascular mortality	7-year all-cause mortality: 12.7% for invasive therapy and 13.4% for conservative therapy (adjusted HR 1.00, 95% CI 0.85–1.18) 7-year cardiovascular mortality: 6.4% for invasive therapy and 8.6% for conservative therapy (adjusted HR 0.78, 95% CI 0.63–0.96) 7-year non-cardiovascular mortality: 5.6% invasive therapy and 4.4% for conservative therapy (adjusted HR 1.44, 95% CI 1.08–1.91)	19
REVIVED-BCIS2 (2022)	Patients (*n*=700) with LVEF ≤35%, extensive CAD and demonstrable viability in ≥4 dysfunctional myocardial segments amenable to PCI	PCI plus OMT vs OMT alone	Composite of death from any cause or hospitalization for heart failure	Primary end point (41 months): 37.2% for PCI group and 38.0% for OMT (HR 0.99, 95% CI 0.78–1.27; *P*=0.96)	20
PREVENT (2024)	Patients (*n*=1,606) aged ≥18 years with stable CAD or ACS with stenosis >50% and FFR ≥0.80 meeting ≥2 criteria for vulnerable plaque definition: minimal lumen area ≤4.0 mm^2, plaque burden >70%, thin-cap fibroatheroma by OCT or IVUS, lipid-rich plaque by near-infrared spectroscopy	PCI plus OMT vs OMT alone	Composite of death from cardiovascular causes, target-vessel MI, ischaemia-driven target-vessel revascularization or hospitalization for unstable or progressive angina	Primary end point at 2 years: 0.4% for PCI group and 3.4% for OMT (HR 0.11, 95% CI 0.03–0.36; *P*=0.0003)	26

Medical therapy was 'optimal' for the time that each trial was conducted. As new medications are developed, the definition of OMT changes. ACIP, Asymptomatic Cardiac Ischemia Pilot; ACS, acute coronary syndrome; AVERT, Atorvastatin versus Revascularization Treatments; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAG, coronary artery angiography; CCS, Canadian Cardiovascular Society; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; CVA, cerebrovascular accident; ECG, electrocardiogram; FAME 2, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2 study; FFR, fractional flow reserve; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; ISCHEMIA-EXTEND, ISCHEMIA ongoing long-term follow-up; IVUS, intravascular ultrasonography; JSAP, Japanese Stable Angina Pectoris Study; LAD, left anterior descending coronary artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; MASS, Medicine, Angioplasty or Surgery Study; MI, myocardial infarction; NAMIS, non-acute myocardial ischaemic syndromes; NS, not significant; OCT, optical coherence tomography; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PREVENT, Preventive PCI or Medical Therapy Alone for Vulnerable Atherosclerotic Coronary Plaque; REVIVED-BCIS2, Revascularization for Ischaemic Ventricular Dysfunction; RITA-2, Randomized Intervention Treatment of Angina; T2DM, type 2 diabetes mellitus; TIME, Trial of Invasive versus Medical therapy in Elderly patients.

in the group assigned to medical therapy (although this treatment was by no means similar to contemporary, multifaceted OMT).

In 2007, the COURAGE trial[36,53] confirmed the short-term benefits of PCI on angina symptoms, with overall rates of angina significantly lower with PCI than with OMT for most of the follow-up period, although after 5 years, the rates of freedom from angina were similar in the two group. Similarly, in the FAME 2 trial[41], those who underwent FFR-guided PCI had significantly less angina up to 3 years after randomization than those who received OMT. However, after 5 years of follow-up, the difference between the groups was no longer significant[44].

The benefits of invasive treatment on angina relief were replicated in the landmark ISCHEMIA trial, which is the largest RCT in the NAMIS population to date[18]. The ISCHEMIA trial[18] showed that Seattle Angina Questionnaire (SAQ) summary scores were significantly higher at 3, 12 and 36 months among patients who underwent invasive treatment plus OMT than among those who received OMT alone. The magnitude of the improvement in SAQ scores in the overall cohort was modest. The greatest benefits were observed in the 21% of patients who had frequent (daily or weekly) angina at baseline, whereas older patients (aged ≥75 years) derived less improvement in angina-related health status than younger patients (aged <75 years)[54]. Of note, complete revascularization was associated with better improvement in health status[55].

Although these trials showed improvement in angina symptoms, a major criticism has been that they were all unblinded comparisons, meaning that the placebo effect, which is known to be greater for invasive than non-invasive treatments, could have led to large improvements in patient-reported symptoms[56]. To overcome this potential limitation, the double-blind, sham (placebo)-controlled ORBITA trial[24] was conducted in 200 patients with NAMIS (angina and ≥70% single-vessel CAD). Patients were randomly assigned to PCI or a sham procedure, in which they were sedated for ≥15 min on the catheterization table using auditory isolation with headphones, and coronary catheters were withdrawn without intervention[24]. Before randomization, patients underwent a 6-week period of medical optimization and were up-titrated to an average of three anti-anginal agents. No significant difference was reported in the primary end point of improvement in exercise time (a between-group difference of 17 s at 6 weeks) or in the other patient-centred end points of angina or QoL[24], thereby raising concerns about a placebo-dependent effect on health status associated with PCI.

Table 2 | Trials of invasive therapy compared with OMT in patients with NAMIS (angina and QoL end points)

Trial (year)	Key inclusion criteria	Interventions	Outcome measures	Outcome point estimates	Ref.
ACME-I (1992)	Patients (n=107) with stable angina, positive exercise stress and angiographic 70–99% stenosis in the proximal two-thirds of one major coronary artery	PTCA vs medical therapy	Changes in exercise tolerance (baseline and follow-up), frequency of angina and use of nitroglycerin	At 6 months: 64% of PTCA group free from angina vs 46% of the medical therapy group (P<0.01) Total duration of exercise: 2.1-min increase for PTCA group vs 0.5-min increase for medical therapy group (P<0.0001) PTCA group able to exercise for longer without angina than medical therapy group (P<0.01)	51
ACME-II (1997)	Patients (n=328) with a history of angina, AMI within 3 months or positive exercise ECG. Angiographically: ≥70% stenosis in the proximal two-thirds of one or two coronary arteries. Candidate for CABG surgery or PCI	PTCA vs medical therapy	Symptoms, treadmill performance and QoL score	At 6 months in double-vessel disease for PTCA vs medical therapy: similar improvement in exercise duration (+1.2 min vs 1.3 min; P=0.89), freedom from angina (53% vs 36%; P=0.09) and improvement in QoL score (+1.3 vs 4.4; P=0.32) At 6 months in single-vessel disease: greater benefit of PTCA by these criteria (P=0.0001–0.02)	88
RITA-2 (1997)	Patients (n=1,018) aged ≥18 years with clinically significant stenosis in ≥1 major epicardial vessel	Balloon angioplasty vs medical therapy	Angina assessed with the CCS classification and documentation of anti-anginal drug use	At 3 months after randomization: 16.5% excess of grade 2+ angina in medical therapy group (P<0.001)	32
TIME (2001)	Patients (n=305) aged ≥75 years with chest pain refractory to ≥2 anti-anginal agents irrespective of previous revascularizations	Revascularization (PCI or CABG surgery) vs medical therapy	QoL questionnaire containing questions from SF36, the DASI and the Rose questionnaire	After 6 months: decrease in angina severity and increase in QoL in both groups (significantly greater improvements after revascularization)	52
COURAGE (2007)	Patients (n=2,287) with stable CAD, initial CCS class IV angina stabilized medically, and either (1) ≥70% stenosis in ≥1 vessel with objective ischaemia (either substantial ST segment depression or T wave inversion or inducible ischaemia with exercise or pharmacological stress), or (2) ≥1 stenosis of ≥80% and classic angina without provocative testing	PCI plus medical therapy vs medical therapy alone	Angina assessed by the CCS classification	Freedom from angina at 1 year: 66% for PCI vs 58% for medical therapy (P<0.0001) At 3 years: 72% for PCI group vs 67% for medical therapy (P<0.02) At 5 years: 74% for PCI vs 72% for medical therapy (P=NS)	36
FAME 2 (2012)	Patients (n=888) who were clinically stable with CAD in one, two or three vessels suitable for PCI with ≥1 stenosis with FFR ≤0.80	FFR-guided PCI plus medical therapy vs medical therapy alone	Angina assessed by the CCS classification	Patients with CCS II–IV angina at 30 days: 11.1% for PCI vs 28.9% for medical therapy (RR 0.38, 95% CI 0.28–0.53; P<0.001) At 6 months: 8.8% for PCI vs 19.2% for medical therapy (RR 0.46, 95% CI 0.28–0.74; P=0.002) At 12 months: 2.4% for PCI vs 16.2% for medical therapy (RR 0.15, 95% CI 0.02–1.19; P=0.07)	41
ORBITA (2017)	Patients (n=200) aged 18–85 years with stable angina or angina equivalent and ≥1 lesion angiographically ≥70% in a single vessel amenable to PCI	PCI plus OMT vs sham (placebo) procedure plus OMT	Between-group difference in exercise time increment	No significant difference in exercise time increment between groups (PCI minus placebo 16.6 s, 95% CI −8.9 to 42.0 s; P=0.200)	24
ISCHEMIA-Health Status Outcomes (2020)	Patients (n=5,179) with stable CAD, moderate or severe reversible ischaemia on imaging stress or severe ischaemia on exercise stress tests	PCI plus OMT (invasive) vs OMT alone (conservative)	Symptoms, function and QoL	SAQ summary scores at 3, 12 and 36 months were 4.1 points (95% CI 3.2–5.0), 4.2 points (95% CI 3.3–5.1) and 2.9 points (95% CI 2.2–3.7) higher, respectively, with the invasive compared with the conservative strategy Differences were larger among participants with more frequent angina at baseline	18
ORBITA-2 (2023)	Patients (n=301) with angina, ≥1 severe stenosis and evidence of ischaemia on non-invasive imaging or invasive testing, who were clinically suitable for PCI	PCI plus OMT vs sham (placebo) procedure plus OMT	Angina symptom score	At 12 weeks: mean angina symptom score 2.9 for PCI vs 5.6 for sham (OR 2.21, 95% CI 1.41–3.47; P<0.001)	25

Medical therapy was 'optimal' for the time that each trial was conducted. As new medications are developed, the definition of OMT changes. ACME-I/II, Angioplasty Compared to Medicine I/II; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DASI, Duke activity score index; ECG, electrocardiogram; FAME 2, Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; FFR, fractional flow reserve; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; NAMIS, non-acute myocardial ischaemic syndromes; NS, not significant; OMT, optimal medical therapy; ORBITA, Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; QoL, quality of life; RITA-2, Randomized Intervention Treatment of Angina 2; SAQ, Seattle Angina Questionnaire; SF36, 36-item short form survey; TIME, Trial of Invasive vs Medical therapy in Elderly patients.

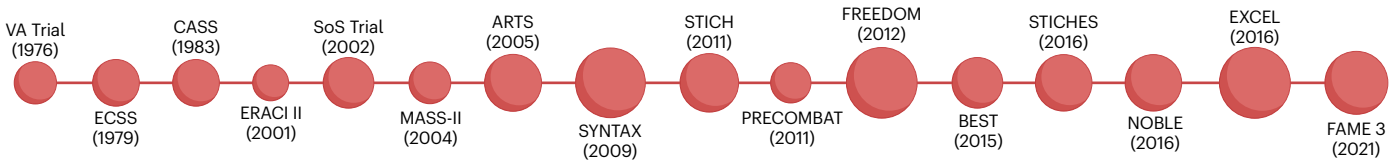

Fig. 2 | Timeline of trials in which CABG surgery was compared with PCI and/or medical therapy in patients with non-acute myocardial ischaemic syndromes. Randomized, controlled trials evaluating coronary artery bypass graft (CABG) surgery versus percutaneous coronary intervention (PCI), medical therapy or both are presented chronologically. The size of each circle is proportional to the sample size of the trial. ARTS[109], Arterial Revascularization Therapies Study; BEST[102], Bypass Surgery and Everolimus-Eluting Stent Trial; CASS[89], Coronary Artery Surgery Study; ECSS[70], European Coronary Surgery Study; ERACI II[94], Argentine Randomized Study: Coronary Angioplasty With Stenting vs Coronary Bypass Surgery in Patients With Multiple-Vessel Disease; EXCEL[73], Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FAME 3 (ref. 11), Fractional Flow Reserve-Guided Percutaneous Coronary Intervention vs Coronary Bypass Surgery in Patients With Multivessel Disease; FREEDOM[108], Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; MASS-II[106], Medicine, Angioplasty, or Surgery Study II; NOBLE[74], Nordic–Baltic–British Left Main Revascularization Study; PRECOMBAT[103], Premier of Randomized Comparison of Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; SoS Trial[110], Stent or Surgery Trial; STICH[21], Surgical Treatment for Ischaemic Heart Failure; STICHES[23], STICH Extension Study; SYNTAX[13], Synergy Between PCI With Taxus and Cardiac Surgery; VA Trial[68], Veterans Administration Cooperative Study.

The ORBITA trial investigators subsequently postulated that the trial might not have shown a significant difference in angina relief or exercise performance between PCI and the sham procedure because of the high number of background anti-anginal medications (OMT) used in the trial, which might have attenuated between-group differences. To address this concern, the 2023 ORBITA-2 trial[25] was conducted in 301 patients with NAMIS and objective evidence of ischaemia, randomly assigned to either PCI or a sham (placebo) procedure[25]. Patients in both groups received background OMT; however, anti-anginal therapy was withdrawn before randomization. Therefore, the ORBITA-2 trial was designed to assess the effects of PCI without concomitant anti-anginal therapy, in contrast to the ORBITA trial, which primarily tested the additive effect of PCI on maximal medical therapy. The primary end point in the ORBITA-2 trial was an angina symptom score. After 12 weeks of follow-up, PCI resulted in a significantly lower angina symptom score (driven by daily anginal episodes and not by daily anti-anginal medication use) compared with the sham procedure[25]. In addition, patients undergoing PCI had a 59.5 s longer treadmill exercise time than patients who underwent the sham procedure[25]. Subsequent post hoc analysis from the ORBITA-2 trial demonstrated that the magnitude of symptomatic improvement after PCI was greatest in patients with the lowest baseline physiological indices by FFR and instantaneous wave-free ratio[57], again highlighting the potentially important role of invasive physiological assessment in identifying those most likely to benefit.

Of note, CABG surgery can achieve greater symptom relief than PCI in patients who are appropriate candidates for surgery. In the SYNTAX trial[58], investigators compared SAQ angina frequency in patients with multivessel CAD who underwent PCI or CABG surgery. Although, in the short term (<5 years), the benefit was similar with either strategy, after 5 years of follow-up, CABG surgery was associated with greater angina relief than PCI, particularly among patients with the highest SYNTAX scores[58].

The totality of evidence shows that PCI and CABG surgery both significantly reduce angina symptoms in patients with NAMIS. However, whether invasive therapy is associated with significant incremental benefit in patients who are receiving maximal anti-anginal therapy remains unclear. Secondary analysis of data from the ORBITA-2 trial has demonstrated that dobutamine stress echocardiography could help to predict which patients are likely to experience symptomatic improvement after PCI[59]. Importantly, however, many patients present without ACS or even stable angina, but have anatomically extensive CAD, which would prompt consideration of invasive treatment even among the most conservative clinicians. These uncertainties underscore the limitations of a largely prescriptive treatment framework or a 'one-size-fits-all' approach to patients with angina, suggesting that treatment should be more nuanced and individualized.

Heterogeneous treatment effects

Several hypotheses have been proposed to explain potential differences in long-term outcomes between CABG surgery and PCI in specific subgroups of patients with NAMIS. One such hypothesis relates to atherosclerotic plaque vulnerability and lesion severity. The majority of MIs are caused by high-risk coronary lesions with <70% stenosis, which are associated with a higher frequency of MI than lesions with >70% stenosis[9,60]. PCI is offered primarily to treat flow-limiting (>70%) stenoses and, therefore, might not reduce cardiovascular events driven by non-obstructive lesions. By contrast, CABG surgery bypasses both flow-limiting and more proximal non-flow-limiting stenoses, thereby reducing the risk of MI and increasing survival. Accordingly, the cardioprotective superiority of CABG surgery is postulated to result from bypass grafts that treat not only culprit lesions (even anatomically complex ones) but also to confer prophylaxis against new proximal disease. By contrast, stents treat only suitable stenotic segments, with no benefit against native CAD progression. Therefore, intervening solely to restore coronary flow (principally with PCI) might not be sufficient to prevent cardiovascular events[10]. Accordingly, three treatment mechanisms of CABG surgery and PCI in the coronary vasculature have been proposed — restoration of coronary flow, reperfusion and infarct prevention through surgical collateralization. To date, the last of these three mechanisms is achievable only through CABG surgery, which could explain the benefits observed with CABG surgery in patients with NAMIS[10] (Fig. 3).

In the 2024 PREVENT trial[26], OMT plus 'preventive' PCI of focal, non-FFR-positive plaques (>50% stenosis) with evidence of vulnerability on intravascular imaging was superior to OMT for the clinical outcome of target-vessel failure (0.4% versus 3.4%; $P = 0.0003$) at

Table 3 | Trials of CABG surgery compared with PCI and/or OMT in patients with NAMIS

Trial/author name (year)	Key inclusion criteria	Intervention	Outcome measures	Outcome point estimates	Ref.
CASS (1983)	Patients (*n*=780) aged ≤65 years with CCS class I or II angina with or without a history of MI, or well-documented MI >3 weeks before randomization, stenosis of ≥70% in the LAD, RCA or LCX or ≥50% in the LMCA	CABG surgery vs medical therapy	Survival at 6 years	Annual mortality: medical therapy 1.6% vs CABG surgery 1.1% (*P*=0.34)	89
The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group (1984)	Patients (*n*=686) with stable angina	CABG surgery vs medical therapy	Long-term survival	All patients, 7-year survival: medical therapy 70% vs CABG surgery 77% (*P*=0.043) All patients, 11-year survival: medical therapy 57% vs CABG surgery 58% Patients without LMD, 7-year survival: medical therapy 72% vs CABG surgery 77% (*P*=0.267) Patients without LMD, 11-year survival: 58% in both groups Patients with impaired LV function, 7-year survival: medical therapy 63% vs CABG surgery 74% (*P*=0.049) Patients with impaired LV function, 11-year survival: medical therapy 49% vs CABG surgery 53%	68
SIMA (2000)	Patients (*n*=121) with symptomatic or silent ischaemia and isolated proximal CAD of the LAD, lesion before the first diagonal branch or ostial lesions, LVEF >45%, vessel size >3.0 mm, consensus between cardiologist and cardiac surgeon about feasibility of both procedures	PCI vs CABG surgery using left IMA (sternotomy and MIDCAB)	Composite of cardiac death, MI or repeat revascularization	Cardiac death, MI or repeat revascularization: PCI 31% vs CABG surgery 7% (RR 4.0, 95% CI 2.0–6.0; *P*<0.001)	90
AWESOME (2001)	Patents (*n*=454) with medically refractory MI and ≥1 risk factor associated with increased 30-day operative mortality and anatomy treatable by either strategy	PCI vs CABG surgery	Survival at 36 months	Survival 36 months: PCI 80% vs CABG surgery 79% (*P*=0.46)	91
Diegeler et al.[92]	Patients (*n*=220) with isolated high-grade lesion ≥75% in proximal LAD, lesion between origin of LCX and first major septal branch	PCI vs MIDCAB	Cardiac death, MI, cardiac death or MI, revascularization of the target vessel, MACE at 6 months, periprocedural complications	Cardiac death: PCI 0% vs MIDCAB 2% (*P*=0.99) MI: PCI 3% vs MIDCAB 5% (RR 1.77, 95% CI 0.41–7.58; *P*=0.68) Cardiac death or MI: PCI 3% vs MIDCAB 6% (RR 2.33, 95% CI 0.34–43.73; *P*=0.5) Revascularization of the target vessel: PCI 29% vs MIDCAB 8% (RR 0.29, 95% CI 0.09–0.65; *P*=0.003) MACE: PCI 31% vs MIDCAB 15% (RR 0.47, 95% CI 0.21–0.89; *P*=0.02)	92
Drenth et al.[93]	Patients (*n*=102) with chronic stable angina pectoris class ≥2, isolated B2 or C lesion of the proximal LAD, eligible for both MIDCAB and PCI	PCI vs MIDCAB	QCA follow-up at 6 months	MIDCAB: stenosis of anastomosis 4% PCI: restenosis 29% (*P*<0.001)	93
ERACI II (2004)	Patients (*n*=450) with multivessel CAD with stable angina (CCS III–IV) despite maximal medical treatment, unstable angina (including post-acute MI angina), no angina or minimal symptoms but a large area of myocardium at risk by exercise testing, ≥70% stenosis in ≥1 epicardial vessel and >50% in other vessels, ULMCA disease if amenable to single-stent procedure according to the interventionalist	PCI vs CABG surgery	Composite of MACE: all-cause death, Q wave MI, stroke and need for repeat revascularization procedures at 30 days, 1 year, 3 years and 5 years	MACE-free survival: PCI 65.3% vs CABG surgery 76.4% (*P*=0.019)	94

Table 3 (continued) | Trials of CABG surgery compared with PCI and/or OMT in patients with NAMIS

Trial/author name (year)	Key inclusion criteria	Intervention	Outcome measures	Outcome point estimates	Ref.
Hong et al.[95]	Patients (*n*=189) with isolated high-grade stenosis (≥70%) of the proximal LAD	PCI vs MIDCAB	Death, MI, repeat target-vessel revascularization, CCS angina class III–IV, periprocedural out comes	Death: PCI 0.0% vs CABG surgery 2.9% (*P*=0.135) MI: PCI 1.7% vs CABG surgery 2.9% (RR 0.73, 95% CI 0.27–1.99; *P*=0.627) Repeat target-vessel revascularization: PCI 2.6% vs CABG surgery 1.5% (RR 1.49, 95% CI 0.27–8.22; *P*=1.00) CCS class III–IV: PCI 2.6% vs CABG surgery 4.4% (RR 0.73, 95% CI 0.32–1.66; *P*=0.671)	95
CARDIA (2009)	Patients (*n*=510) with diabetes mellitus, multivessel CAD or complex single-vessel CAD, recommended coronary revascularization on clinical grounds, reasonable equipoise in the risks and benefits of PCI and CABG surgery reviewed by experienced interventional cardiologist and cardiac surgeon	PCI vs CABG surgery	Composite of death, MI and stroke at 1 year All-cause death at 1 year	Primary end point: PCI 13.0% vs CABG surgery 10.5% (HR 1.25, 95% CI 0.75–2.09) All-cause mortality: PCI 3.2% vs CABG surgery 3.2% (HR 0.98, 95% CI 0.37–2.61)	96
ARTS II (2010)	Patients (*n*=1,812) with de novo multivessel CAD (patients receiving PCI were part of ARTS I and II; patients receiving CABG surgery were part of ARTS I)	PCI vs CABG surgery	MACCE (all-cause death, CVA, non-fatal MI, repeat revascularization)	MACCE: PCI with SES 27.2%, PCI with BMS 41.2%, CABG surgery 20.8% (SES–CABG surgery difference 6.4, 95% CI 1.6– 11.2; SES–BMS difference 14.0, 95% CI 19.3–8.7)	97
Boudriot et al.[98]	Patients (*n*=201) aged 18–80 years with stenosis ≥50% of the ULMCA, with or without additional multivessel CAD, symptomatic or documented myocardial ischaemia	PCI vs CABG surgery	Composite of freedom from MACE (death from any cause, MI, repeat revascularization within 1 year)	Freedom from MACE: PCI 19.0% vs CABG surgery 13.9% (95% CI −5.3 to 15.7, *P*=0.19; criteria for non-inferiority not reached (upper-bound 10.0%))	98
VA CARDS (2013)	Patients (*n*=198) with diabetes mellitus, multivessel CAD including the LAD or isolated proximal LAD CAD, objective evidence of ischaemia for stenoses 50–70%	PCI vs CABG surgery	Composite of all-cause death or non-fatal MI	All-cause mortality or non-fatal MI: PCI 25.3% vs CABG surgery 18.4% (HR 0.85, 95% CI 0.47–1.71)	99
SYNTAX: 5 years, 3VD (2014)	Patients (*n*=1,800) with 3VD, LMD or equivalent one-vessel, two-vessel or three-vessel disease, de novo lesions with ≥50% stenosis, myocardial ischaemia (stable, unstable or silent)	PCI+aspirin+antiplatelet medication on the basis of local clinical practice vs CABG surgery+aspirin+ standard post-intervention care	MACCE at 12 months (all-cause death, stroke, MI, repeat revascularization (non-inferiority)) and individual components of this composite	MACCE at 12 months: PCI 37.5% vs CABG surgery 24.2% (HR 1.70, 95% CI 1.36–2.13) All-cause death, stroke or MI: PCI 22.0% vs CABG surgery 14.0% (HR 1.64, 95% CI 1.22–2.20) Repeat revascularization: PCI 25.4% vs CABG surgery 12.6% (HR 2.24, 95% CI 1.65–3.04)	100
SYNTAX: 5 years, LMD (2014)	Patients (*n*=1,800) with 3VD, LMD or equivalent one-vessel, two-vessel or three-vessel disease, de novo lesions with ≥50% stenosis, myocardial ischaemia (stable, unstable or silent)	PCI+aspirin+antiplatelet medication on the basis of local clinical practice vs CABG surgery+aspirin+standard post-intervention care	MACCE at 12 months (all-cause death, stroke, MI, repeat revascularization (non-inferiority)) and individual components of this composite	MACCE at 12 months: PCI 36.9% vs CABG surgery 31.0% (HR 1.23, 95% CI, 0.95–1.59) All-cause death, stroke or MI: PCI 19.0% vs CABG surgery 20.8% (HR 0.91, 95% CI 0.65–1.27) Repeat revascularization: PCI 26.7% vs CABG surgery 15.5% (HR 1.82, 95% CI 1.28–2.57)	101
BEST (2015)	Patients (*n*=880) with multivessel CAD, >70% lesions in at least two major vessels and in at least two separate territories (LAD, LCX, RCA), symptoms of angina and/or objective myocardial ischaemia	PCI+aspirin indefinitely and clopidogrel for ≥12 months vs CABG surgery+medications selected according to the policy of the institution or physician	Composite of death, non-fatal MI and ischaemia-driven target-vessel revascularization (non-inferiority of PCI to CABG surgery) at 2 years	Composite end point: PCI 11.0% vs CABG surgery 7.9%, absolute risk difference 3.1% (95% CI −0.8 to 6.9; *P*=0.32 for non-inferiority, influenced by more spontaneous MI and more re-revascularization)	102

Table 3 (continued) | Trials of CABG surgery compared with PCI and/or OMT in patients with NAMIS

Trial/author name (year)	Key inclusion criteria	Intervention	Outcome measures	Outcome point estimates	Ref.
PRECOMBAT (2015)	Patients (*n*=600) with left main stenosis >50% with or without additional target lesions >70%, left main lesion and lesions outside LMCA	PCI+aspirin indefinitely+clopidogrel or ticlopidine for ≥1 year vs CABG surgery+medications according to the policy of the institution or the preference of the surgeon	MACCE (composite of death, MI, stroke and ischaemia-driven target-vessel revascularization (non-inferiority of PCI to CABG surgery))	MACCE (ITT): PCI 17.5% vs CABG surgery 14.3% (HR 1.27, 95% CI 0.84–1.90; *P*=0.26) MACCE (as-treated): PCI 19.2% vs CABG surgery 12.0% (HR 1.67, 95% CI 1.09–2.56; *P*=0.017)	103
Blazek et al.[104]	Patients (*n*=130) with single-vessel disease of the proximal LAD with stenosis >50% (multivessel disease only if further coronary vessel stenoses do not require treatment), angina pectoris (CCS I–IV) or asymptomatic if clear signs of ischaemia in the segments supplied by the LAD	PCI+DAPT for ≥12 months vs MIDCAB+aspirin	MACE at 7 years; non-inferiority of PCI to CABG surgery	MACE: PCI 22% vs CABG surgery 12%; difference 0.7 (RR 1.47, 95% CI 0.82–2.62; *P*=0.17)	104
STICHES (2016)	Patients (*n*=1,212) aged ≥18 years, comprising women not of childbearing potential and men, LVEF ≤0.35 measured by CMR ventriculogram, gated SPECT ventriculogram, echocardiography or contrast ventriculogram within 3 months of trial entry, CAD suitable for revascularization	CABG surgery vs medical therapy	All-cause death	CABG surgery 58.9% vs medical therapy 66.1% (HR 0.84, 95% CI 0.73–0.97; *P*=0.02)	23
NOBLE (2016)	Patients (*n*=1,201) with LMD, stable angina, unstable angina or ACS, with ≥50% stenosis or FFR ≤0.80 in left main ostium, mid-shaft or bifurcation, with no more than three additional non-complex lesions	PCI+75 mg clopidogrel daily for 12 months vs CABG surgery	MACCE (all-cause death, non-procedural MI, repeat revascularization or stroke (non-inferiority of PCI to CABG surgery))	MACCE at 1 year: PCI 7.0% vs CABG surgery 7.0% (relative difference: 0.0, 95% CI −2.9 to 2.9; *P*=1.00) MACCE at 5 years: PCI 28.0% vs CABG surgery 18.0% (HR 1.51, 95% CI 1.13–2.00, exceeding the limit for non-inferiority (1.35), for superiority of CABG surgery compared with PCI: *P*=0.0044)	74
LE MANS (2016)	Patients (*n*=105) with LMCA stenosis >50%	PCI vs CABG surgery	All-cause mortality and MACCE at 10 years	All-cause mortality: PCI 21.6% vs CABG surgery 30.2% (HR 1.55, 95% CI 0.71–3.39) MACCE: PCI 52.2% vs CABG surgery 62.5% (HR 1.57, 95% CI 0.90–2.73)	105
SYNTAX: 5 years, QoL (2017)	Patients (*n*=1,800) with 3VD, LMD or equivalent one-vessel, two-vessel or three-vessel disease, de novo lesions with ≥50% stenosis, myocardial ischaemia (stable, unstable or silent)	PCI+aspirin+antiplatelet medication on the basis of local clinical practice vs CABG surgery+aspirin+standard post-intervention care	SAQ health status at 1, 6, 12, 36 and 60 months	SAQ at 1 month (mean difference between PCI and CABG surgery): angina frequency −1.3 (95% CI −3.2 to 0.5), physical limitation −12.0 (95% CI −14.3 to −9.6), QoL −4.8 (95% CI −7.1 to −2.5) SAQ at 1 year: angina frequency 1.7 (95% CI 0.2–3.3), physical limitation 1.2 (95% CI −0.8 to 3.3), QoL 2.5 (95% CI 0.3–4.7) SAQ at 5 years: angina frequency 2.1 (95% CI 0.4–3.8), physical limitation 3.0 (95% CI 0.5–5.4), QoL 1.8 (95% CI −0.5 to 4.2) Evidence from subgroup analyses that CABG surgery had the greatest benefit in patients with a SYNTAX score >22	58
MASS II (2017)	Patients (*n*=579) with multivessel ≥70% stenosis in coronary arteries and documented ischaemia (either by stress testing or stable angina)	PCI vs CABG surgery vs OMT	Non-fatal MI, cardiac death and refractory angina requiring revascularization at 5 years	Non-fatal MI: PCI 17.5%, CABG surgery 10.6%, OMT 17.3% Cardiac death: PCI 16.6%, CABG surgery 18.2%, OMT 19.7% Refractory angina: PCI 9.8%, CABG surgery 5.3%, OMT 3.6% (hazard ratios not reported)	106

Table 3 (continued) | Trials of CABG surgery compared with PCI and/or OMT in patients with NAMIS

Trial/author name (year)	Key inclusion criteria	Intervention	Outcome measures	Outcome point estimates	Ref.
EXCEL (2019)	Patients (*n*=1,905) with ULMCA disease with stenosis ≥70% or, ULMCA disease ≥50% but <70% stenosis with one or more of the following: non-invasive evidence of ischaemia in left main lesion, or stress-induced hypotension or fall in LVEF, or stress-induced transient ischaemic dilatation or thallium/technetium lung uptake, and/or IVUS minimum lumen area ≤6.0 mm^2, and/or FFR ≤0.80, LMD equivalent	PCI+DAPT initiated before PCI and continued for ≥1 year vs CABG surgery+aspirin perioperative±clopidogrel during follow-up (not mandatory)	MACCE (all-cause death, MI or stroke (non-inferiority of PCI to CABG surgery))	MACCE at 30 days: PCI 4.9% vs CABG surgery 7.9% (HR 0.61, 95% CI 0.42–0.88; *P*=0.008) MACCE at 3 years: PCI 15.4% vs CABG surgery 14.7% (difference 0.7, upper 97.5% confidence limit 4.0; *P*=0.02 for non-inferiority; HR 1.00, 95% CI 0.79–1.26; *P*=0.98 for superiority)	73
SYNTAX: 10 years (2019)	Patients (*n*=1,800) with 3VD, LMD or equivalent one-vessel, two-vessel or three-vessel disease, de novo lesions with ≥50% stenosis, myocardial ischaemia (stable, unstable or silent)	PCI+aspirin+antiplatelet medication on the basis of local clinical practice vs CABG surgery+aspirin+standard post-intervention care	All-cause mortality at 10 years	All-cause mortality: PCI 27.0% vs CABG surgery 24.0% (HR 1.17, 95% CI 0.97–1.41)	107
FREEDOM (2019)	Patients (*n*=1,900) with type 1 or type 2 diabetes mellitus, multivessel CAD ≥70% lesions in at least two major vessels and in at least two separate territories (LAD, LCX, RCA)	PCI vs CABG surgery	Composite of all-cause death, non-fatal MI and stroke at 5 years	Composite end point (ITT, whole cohort): PCI 24.3% vs CABG surgery 18.3% (HR 1.36, 95% CI 1.07–1.74; *P*=0.01)	108
FAME 3 (2022)	Patients (*n*=1,500) with 3VD	FFR-guided PCI with ZES vs CABG surgery	MACCE (defined as all-cause death, MI, stroke or repeat revascularization) at 1 year	MACCE: PCI 10.6% vs CABG surgery 6.9% (HR 1.5, 95% CI 1.1–2.2; *P*=0.35 for non-inferiority)	11

Medical therapy was 'optimal' for the time that each trial was conducted. As new medications are developed, the definition of OMT changes. 3VD, three-vessel disease; ACS, acute coronary syndrome; ARTS, Arterial Revascularization Therapies Study; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; BEST, Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; BMS, bare-metal stents; CABG, coronary artery bypass graft; CAD, coronary artery disease; CARDIA, Coronary Artery Revascularization in Diabetes; CCS, Canadian Cardiovascular Society; CMR, cardiac magnetic resonance imaging; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; ERACI, Argentine Randomized Study: Coronary Angioplasty with Stenting vs. Coronary Bypass Surgery in Patients with Multivessel Disease; EXCEL, Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FAME, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FFR, fractional flow reserve; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; IMA, internal mammary artery; ITT, intention-to-treat; IVUS, intravascular ultrasonography; LAD, left anterior descending artery; LCX, left circumflex artery; LE MANS, Left Main Coronary Artery Stenting; LMCA, left main coronary artery; LMD, left main disease; LV, left ventricular; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; MASS II, Medicine, Angioplasty, or Surgery Study II; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass; NAMIS, non-acute myocardial ischaemic syndromes; NOBLE, Nordic–Baltic–British Left Main Revascularization Study; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; QCA, quantitative coronary angiography; QoL, quality of life; RCA, right coronary artery; RR, relative risk; SAQ, Seattle Angina Questionnaire; SES, sirolimus-eluting stents; SIMA, Surgical Intervention versus Medical Therapy in Angina; SPECT, single-photon emission computed tomography; STICHES, Surgical Treatment for Ischemic Heart Failure Extended Study; SYNTAX, Synergy Between PCI with Taxus and Cardiac Surgery; ULMCA, unprotected left main coronary artery; VA CARDS, Veterans Affairs Coronary Artery Revascularization in Diabetes Study; ZES, zotarolimus-eluting stents.

2 years among patients with NAMIS. However, most of this benefit was driven by a reduction in subsequent ischaemia-driven revascularization and hospitalization for unstable angina, without reductions in the rates in MI or cardiac death[26]. These findings have several caveats: the trial had lower than expected event rates, the open-label design might have influenced the need for revascularization, and the imbalance in dual antiplatelet therapy use might have favoured the preventive PCI group. Several trials of selected high-risk patients with vulnerable plaques or chronic total occlusions (such as the ORBITA-CTO Pilot[61], ORBITA-MOON[62] and PRESENT[63] trials) are ongoing to build on the findings from the PREVENT trial, and to determine whether pre-emptive PCI reduces the risk of cardiac death or MI. Importantly, the PREVENT trial and these ongoing trials did not include a CABG surgery group as a comparator — a treatment strategy that has the potential to reduce prognostically important clinical events further. For these many reasons, equipoise in this domain should continue to guide considerations for both the design and execution of future trials.

Invasive therapy in high-risk subgroups

PCI has largely not been associated with significant reductions in mortality or cardiovascular events in the absence of acute ischaemia. However, CABG surgery has produced strong evidence of clinical benefit in patients with high-risk NAMIS, including those with diabetes, LMCAD, complex triple-vessel disease or reduced LV function[11–15] (Table 3). Trials supporting the benefit of surgical revascularization in these subgroups reveal a pathomechanistic pattern, which was first described for CABG surgery in 2019 (ref. 9) and extended to all invasive treatments of CAD in 2021 (ref. 10). A consistent finding is that CABG surgery benefits patients with complex anatomical epicardial CAD, because these individuals often have additional clinical comorbidities that confer increased risk. Patients in high-risk subgroups might derive greater treatment benefit from CABG surgery, owing specifically to the inherent collateralization effect it confers, as discussed in the preceding section. Although this benefit must be weighed against the potentially increased surgical risk, 30-day mortality after CABG

surgery is almost identical to that for PCI in randomized trials[64] and risk-adjusted registry analyses[65].

LMCAD and multivessel CAD

The role of invasive therapy in LMCAD remains one of the last frontiers in treating patients with NAMIS, and uncertainty persists despite advances in OMT, stent technology and surgical techniques[66,67]. As early as the mid-1970s, 686 patients with NAMIS were enrolled in the Veterans Administration Cooperative Studies Program Trial and randomly assigned to either CABG surgery or medical therapy (consisting only of aspirin, nitrates and β-blockers). A subgroup of 113 patients had clinically significant stenosis of the left main coronary artery[64]. This study showed that survival at 24 months was higher, and the angina score was better, with CABG surgery than with medical therapy alone. After 11 years of follow-up, patients with LMCAD maintained a survival benefit from CABG surgery[68]. In 1979, the European Coronary Surgery Study group reported no significant difference in mortality at 2 years among 768 men with NAMIS randomly assigned to CABG surgery or medical therapy alone[69]. However, in the subset of patients with three-vessel disease, survival was significantly better with CABG surgery. After an extended period of follow-up (5–8 years), survival was higher in the overall population receiving surgery, and angina relief was also greater with CABG surgery than with medical therapy[70]. Subsequently, the NIH-funded Coronary Artery Surgery Study[71] did not demonstrate a reduction in mortality in 768 patients randomly assigned to surgical or medical therapy. However, a subgroup analysis of patients in this trial with a LVEF of 35–49% (nearly half of whom had triple-vessel CAD) showed an increase in survival with CABG surgery at 7 years. In 2004, the small, single-centre MASS-II trial[72] involving 611 patients with stable angina provided data supporting the role of CABG surgery to improve anginal symptoms in patients with multivessel disease.

In 2016, the EXCEL trial[73] showed similar outcomes with PCI or CABG surgery in patients with LMCAD and low or intermediate SYNTAX scores. However, these findings were discordant with those in the NOBLE trial[74], published in the same month, which showed that CABG surgery was superior to PCI for LMCAD, irrespective of SYNTAX score. Real-world data from the Interventional Research Incorporation Society–Left MAIN Revascularization Registry published in 2017 suggest that either PCI or CABG surgery is associated with lower mortality in patients with LMCAD than OMT alone[75].

Reduced LVEF

Early trials in patients with high-risk NAMIS seemed to favour CABG surgery as an initial invasive treatment strategy over medical therapy alone. However, one major criticism is that these trials were conducted before the advent of contemporary, guideline-directed, disease-modifying medical therapy targeted towards residual dyslipidaemic, glycaemic, metabolic and inflammatory risk reduction. In addition, although an increasing proportion of patients with LV systolic dysfunction were being referred for CABG surgery in clinical practice, early trials excluded patients with an LVEF of ≤35%[71]. To overcome these limitations, the STICH trial[21] investigators randomly assigned 1,212 patients with an LVEF of ≤35% and CAD eligible for surgical revascularization to medical therapy either alone or combined with CABG surgery. During follow-up (median 56 months), there was no significant difference between the two groups in the primary outcome of death from any cause. However, patients assigned to CABG surgery had lower rates of the composite outcome of death from any cause or hospitalization for cardiovascular causes[21]. Furthermore, a potential increase in survival in patients with demonstrable myocardial viability was reported, although this improvement was no longer significant after adjustment for baseline variables[22]. This observation of clinical benefit has not been universal across all patients or trials. Methodological differences in viability assessment, such as testing modality (dobutamine echocardiography, single-photon emission CT or PET), ischaemic thresholds and timing of surgery might have contributed to

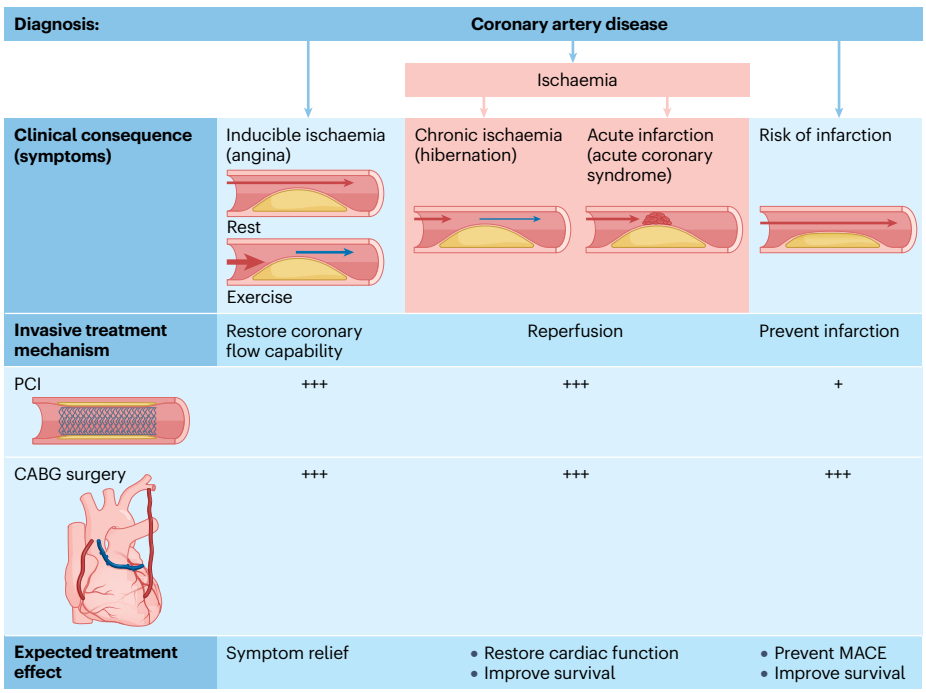

Fig. 3 | Treatment effects of PCI and CABG surgery in coronary artery disease. The clinical consequences of coronary artery disease and the relative effectiveness of the mechanisms underlying percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery to produce the expected treatment effect. MACE, major adverse cardiac events. Figure adapted with permission from ref. 11, Elsevier.

the discrepant findings between studies[22,76]. In STICHES[23] — an extended follow-up study (median 9.8 years) of the STICH trial — both the primary (all-cause mortality) and secondary outcome events occurred in fewer patients undergoing CABG surgery than in those receiving OMT, confirming the benefit of CABG surgery in patients with complex CAD and reduced LVEF.

With the data supporting CABG surgery for patients with severe ischaemic cardiomyopathy (LVEF <35%)[21,22], PCI was expected to offer similar effects by eliminating obstructive lesions in patients with reduced LVEF and documented inducible ischaemia. However, the REVIVED-BCIS2 trial[20], published in 2022 and involving 700 patients with CAD and an LVEF of <35% (14% of whom had LMCAD), did not demonstrate significantly lower rates of all-cause death or hospitalization for heart failure after PCI than with OMT. Although QoL scores at 6 and 12 months favoured PCI, these differences had attenuated by 24 months. The null results of the REVIVED-BCIS2 trial reconfirmed scepticism about whether viability tests can reliably predict which patients have myocardial hibernation and will benefit from invasive therapy. The fact that PCI did not provide incremental benefit in improving LV function over OMT parallels the findings of the STICH trial, in which CABG surgery did not improve LV function, even in patients with documented myocardial viability. The 2025 combined patient-level analysis of the REVIVED-BCIS2 and STICHES trials showed that patients in the REVIVED-BCIS2 trial, who were treated with contemporary medical therapy and more frequently had implantation of a cardioverter–defibrillator, had better survival than patients treated with older medical therapy in the STICHES trial[77]. Whether CABG surgery would provide benefits above and beyond contemporary medical therapy remains unclear[78].

Contemporary trials comparing PCI and CABG surgery in patients with reduced LVEF are underway (such as the STICH3 trial[79]). With improved heart failure management and outcomes, and intriguing secondary observations from the REVIVED BCIS2 trial questioning the link between myocardial viability and the benefit of PCI[80], it remains uncertain whether invasive management of patients with ischaemic cardiomyopathy should be routinely pursued, even when myocardial viability is present[81].

Diabetes mellitus

Patients with diabetes comprise a substantial proportion of the NAMIS population in revascularization trials. In the ISCHEMIA trial[82], 42% of those enrolled had diabetes, and this condition was associated with a 49% increase in the risk of death or MI. However, in a secondary analysis of those with diabetes, no significant differences were found between treatment groups in any of the evaluated outcomes, other than a non-significant trend towards benefit with invasive treatment in patients with the most severe coronary anatomy (Duke 6)[82]. In the BARI-2D trial, in which patients with diabetes were randomly assigned to either OMT or invasive therapy (PCI or CABG surgery), no significant differences in survival were found in either stratum (PCI versus OMT or CABG surgery versus OMT)[40], even in those with elevated plasma levels of troponins[38,40]. However, the incidence of major adverse cardiovascular events, particularly for the end point of MI, was found to be lower with CABG surgery than with OMT[40]. In the FREEDOM trial[14], in which patients with diabetes and multivessel disease were randomly assigned to either CABG surgery or PCI, CABG surgery was associated with a reduced rate of cardiovascular events (death, stroke and MI) at 5 years, driven by reductions in death and MI, albeit with an increased incidence of stroke. Accordingly, the relative benefits of PCI and CABG surgery in patients with diabetes remains an important area of ongoing clinical study[38].

The evolution of OMT

Although our primary focus in this Review was on the literature guiding invasive treatment strategies, the foundational platform of care for all patients with NAMIS is the comprehensive use of OMT, which has advanced substantially in the past two decades. Although early trials, such as COURAGE, incorporated aspirin, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and lipid-lowering therapies, modern OMT now encompasses an even broader array of therapeutic options. Antiplatelet therapy with aspirin remains standard, whereas high-intensity statins are the cornerstone of lipid management, with ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors available for patients who do not attain the target plasma level of LDL cholesterol despite maximal statin therapy[83]. Blood pressure control is crucial, with a target of <130/80 mmHg or, ideally, <120/80 mmHg for most patients with NAMIS and hypertension[83]. Guideline-directed agents include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers for patients with compelling indications, such as diabetes or heart failure with reduced LVEF, supplemented by calcium channel blockers, mineralocorticoid receptor antagonists, nitrates, ranolazine and thiazide diuretics as needed and if tolerated[83]. For patients with diabetes, sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists are now standard components of cardiovascular risk reduction, tailored according to comorbid conditions, such as heart failure or chronic kidney disease[83].

Despite robust evidence, the real-world implementation of OMT remains both inconsistent and underutilized, reinforcing the importance of combating therapeutic inertia[84]. The 2023 American multi-society guidelines for the management of patients with chronic CAD detail the classes of recommended therapies[83], and this topic has been comprehensively discussed[85].

Shared clinical decision making

For most patients with NAMIS, data derived from multiple RCTs over the past three decades have been largely concordant. Evidence for significant reductions in mortality or cardiovascular events with PCI is lacking compared with a regimen of contemporary, multifaceted OMT alone. However, evidence from RCTs does support the benefit of PCI above and beyond medical therapy for angina relief and QoL improvement, although not conclusively when compared with multifaceted OMT among patients who can tolerate it. What priority to give to PCI over careful up-titration of anti-anginal medication and intensive OMT use remains an unresolved question and should be discussed in shared decision making with patients. However, reasonable arguments exist not to pursue PCI as the primary modality for symptom relief before optimization of medical therapy in a large proportion of patients[85].

In selecting patients with NAMIS who might benefit from invasive therapy, trial evidence supports the use of CABG surgery principally in those with high-risk features — symptomatic LMCAD or multivessel disease with or without diabetes or LV systolic dysfunction. In patients with or without anginal symptoms, appropriate surgical risk, anatomy amenable to CABG surgery and an LVEF of ≤35%, referral for surgery is an appropriate option[78]. However, equipoise for the benefits of CABG surgery in asymptomatic patients with LMCAD or multivessel disease persists, and contemporary data comparing CABG surgery with modern OMT in these high-risk subgroups (including in patients with

LMCAD) are still lacking. The available data from RCTs do not support routine ischaemia or myocardial viability testing to guide invasive treatment selection.

In summary, the totality of RCT-based evidence points towards the need for physicians and patients to engage in shared clinical decision making on whether to proceed with invasive management. A nuanced and objective discussion of the potential risks and benefits of undergoing an invasive procedure with or without OMT is crucial to achieve truly informed decisions. One such example of a structured framework to facilitate and standardize shared decision making was developed based on outcomes from the ISCHEMIA trial[86]. This tool integrates patient-reported QoL, physical function and angina frequency to generate personalized estimates of treatment benefit to model the likelihood of survival, angina relief and procedural risks associated with an invasive versus a conservative strategy. The final tool includes visual displays of risk, symptom burden scales and value clarification questions to guide more structured clinician–patient conversations.

Conclusions

Scientific evidence supports the initiation and maximization of OMT as the first-line therapeutic approach for most patients with NAMIS, although physicians should carefully consider selected patients who might benefit from invasive management. Patients with persistent symptoms, a particularly active lifestyle and those who cannot tolerate up-titration of medications due to unacceptable adverse effects or who are unwilling to undergo up-titration (particularly with non-complex CAD) are candidates for early PCI to improve QoL. All patients should be counselled on procedural risks and be made aware that continuing OMT, especially with lipid-lowering and antihypertensive drugs, remains an important cornerstone of treatment regardless of whether an invasive approach is chosen. Selecting appropriate, high-risk patients who would benefit from CABG surgery continues to be supported by the evidence for improved event-free survival in these groups (even in rare cases in which high anatomical complexity is present in patients without symptoms). Ultimately, shared clinical decision making between the patient and the physician is paramount. Future prospective studies are warranted, both to define subsets of patients with NAMIS who might benefit from invasive therapies and to further elucidate the mechanisms by which clinical benefit is derived.

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N.C. and W.E.B. researched data for the article. All the authors discussed its content. N.C., R.D.C., T.D. and W.E.B. wrote the manuscript. All the authors reviewed/edited the manuscript before submission.

Competing interests

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